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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/716,189	11/17/2003	Elizabeth Nardin	05986/100B615-US2	5841

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EXAMINER	
GRUN, JAMES LESLIE	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 10/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/716,189	NARDIN ET AL.	
	Examiner	Art Unit	
	James L. Grun	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/17/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The disclosure is objected to because of the following informalities: the entry of "SEQ ID NO:" identifiers must be made for every appearance of sequences in the description or claims of the patent application, e.g. on pages 6, 9, and 19 the identifiers are not present. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

Claims 1-4, 6-10, and 17-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant discloses a particular 20 amino acid residue peptide from the circumsporozoite protein of an isolate of *Plasmodium falciparum*, i.e. SEQ ID NO: 3, as a "universal" T-cell epitope that binds to a multiplicity of MHC molecules. In addition, the related sequences in

other *P. falciparum* isolates or other malarial parasite species which share the purported MHC class II molecule-anchoring motif of the peptide, i.e. the identical pattern of aliphatic and aromatic residues at positions 2, 3, 6, 10, and 14 of the peptide, are taught for use in the invention (see ¶ [0029]). However, the disclosure of a limited number of epitopes, and the teaching of methods to find other such epitopes of unpredictable structures, are not found to adequately describe or broadly support compositions containing any other "universal epitope" or epitopes "consisting essentially" of a sequence, when this is meant to encompass deletions and substitutions within a given sequence. Numerous changes can be made to the peptide sequence as encompassed by the instant claims and the effect of such changes on the immune response elicited thereby would seem entirely unknown and unpredictable as it is notoriously well known in the art that even single amino acid changes in a peptide, even those considered "conservative" with regard to peptide structure, can have profound effects on the immunogenicity/antigenicity of such an altered peptide, and/or sometimes even upon the MHC binding of such a peptide, as compared to the original. Absent such disclosure or predictability of functional modified related peptides, one would have no assurance of success with any peptide related to that having the sequence or motif of SEQ ID NO: 3 other than one having the sequence of SEQ ID NO: 3 or one having the motif of aliphatic and aromatic residues at positions 2, 3, 6, 10, and 14 of SEQ ID NO: 3 **as well as** the sequence as found in all the corresponding positions of the peptide as present in the circumsporozoite protein in another *P. falciparum* isolate or malarial parasite. The disclosure of a research plan allowing another to identify what is claimed as the invention, with further unguided unpredictable experimentation, is not found to provide adequate description or guidance to any particular epitopic structures, other than the single disclosed epitope and those in

other *P. falciparum* isolates or other malarial parasite species which share the purported MHC class II molecule-anchoring motif of the peptide epitope, which function in the invention. Note that an enabling disclosure for the preparation and use of one or only a few analogs of a product does not enable all possible analogs where the characteristics of the analogs are unpredictable. Amgen Inc. v. Chugai Pharmaceutical Co. Ltd. (18 USPQ 2d 1027 (CAFC 1991)). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant is reminded that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. In the absence of any guidance other than to the use of SEQ ID NO: 3 or corresponding sequences in other *Plasmodium* circumsporozoite proteins having the class II molecule binding motif, one would not know or be able to predict or envision what structure or modifications were important for function, particularly for the elicitation of anti-malarial responses. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that a molecule is part of the invention and a reference to a potential method of isolating it. The molecule itself is required. Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of molecules by only their functional activity does not provide an adequate written description of the genus. The court indicated that although applicants are not required to disclose every species encompassed by a genus, the description of

a genus is achieved by the recitation of a representative number of molecules falling within the scope of the claimed genus.

Therefore only the sequence of SEQ ID NO: 3 or one having the motif of aliphatic and aromatic residues at positions 2, 3, 6, 10, and 14 of SEQ ID NO: 3 **as well as** the sequence as found in all the corresponding positions of the peptide as present in the circumsporozoite protein in another *P. falciparum* isolate or malarial parasite, but not the full breadth of the claims, meets the written description and enablement provisions of 35 U.S.C. 112, first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1-20, "diverse genetic backgrounds" is not clear as to what applicant intends as encompassed. The examiner would suggest --having many diverse major histocompatability complex (MHC) Class II molecules--.

In claims 1-4, 7-10, and 12, "malaria-derived" is vague and indefinite as to what is encompassed as the specification teaches that a sequence "derived from" an organism needs merely to be found "in part" within a parasite polypeptide and it is not clear what constitutes a

"part", e.g. it is not clear how many amino acid residues in sequence (2, 10, 20?) are sufficient to be a part of another sequence.

Claims 6 and 17-20 are vague and indefinite in the use of a peptide "consisting essentially of the sequence" because, in view of the definition in the specification regarding amino acid deletions or substitutions (¶ [0022]), one would not be apprised of what peptides were encompassed within the metes and bounds of applicant's intended invention.

In claims 2, 4, and 12, "the" production lacks antecedent basis.

In claims 9, 15, and 19, "the propagation" lacks antecedent basis.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in-
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent,
except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language;

Claims 1-4 and 7-10 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Calvo-Calle et al. (J. Immunol. 150: 1403, 1993).

Calvo-Calle et al. disclose a multiple antigen peptide system comprising a B cell epitope ($(NANP)_3$) and a universal T cell epitope (CS.T3) of the circumsporozoite protein of

Plasmodium falciparum. The system was incorporated into a vaccine composition and was administered to mammals of diverse genetic backgrounds. Calvo-Calle et al. also suggest the T1 epitope, SEQ ID NO: 4 as instantly disclosed, in MAPS with B cell epitopes and other T cell epitopes (see e.g. page 1411).

Claims 1-4 and 7-10 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Herrera et al. (Inf. Imm. 60: 154, 1992).

Herrera et al. disclose a fusion protein immunogen comprising B cell epitopes of a merozoite protein and a universal T cell epitope (CS.T3) of the circumsporozoite protein of *Plasmodium falciparum*. The immunogen was incorporated into a vaccine composition and was administered to mammals of diverse genetic backgrounds. A fusion protein is considered herein as a multiple antigen peptide.

Claims 1, 2, 5-7, 9-13, and 15-20 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Moreno et al. (J. Immunol. 151: 489-499, 1993).

Moreno et al. disclose vaccination with irradiated sporozoites which inherently comprise peptides as instantly claimed.

Claims 1-20 are rejected under 35 U.S.C. § 102(e)(2) as being clearly anticipated by De Wilde et al. (U.S. Pat. No. 5,928,902), and, if necessary, further in light of the instant disclosure and/or Nardin et al. (Ann. Rev. Immunol. 11: 687, 1993).

De Wilde et al. disclose a hybrid protein immunogen comprising B cell epitopes ($(NANP)_{\geq 4}$; see SEQ ID NO: 3, aa residues 7-78) and the T cell epitope as instantly claimed (see SEQ ID NO: 3, aa residues 124-143), inherently a universal T cell epitope (if necessary, in light of the instant disclosure and/or Nardin et al.), of the circumsporozoite protein of *Plasmodium falciparum*. The immunogen was incorporated into a vaccine composition and was administered to mammals of diverse genetic backgrounds (see columns 13-16). The hybrid protein of the reference is considered herein as a multiple antigen peptide.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> (c) Subject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Tam et al. (WO 90/11778) in view of Good et al. (J. Exp. Med. 164: 655, 1985) and Nardin et al. (Ann. Rev. Immunol. 11: 687, 1993), and, if necessary, further in view of either or both of Rose et al. (WO 94/25071) or Rose et al. (Molecular Immunology 32: 1031, 1995).

Claims 1-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Calvo-Calle et al. (J. Immunol. 150: 1403-1412, 1993) in view of Good et al. (J. Exp. Med. 164: 655, 1985) and Nardin et al. (Ann. Rev. Immunol. 11: 687, 1993), and, if necessary, further in view of either or both of Rose et al. (WO 94/25071) or Rose et al. (Molecular Immunology 32: 1031, 1995).

Tam et al. (WO 90/11778) teach a multiple antigen peptide system (MAP) for immunogenic vaccine compositions (see e.g. pages 14-16) comprising a dendritic polymer core, e.g. of branched poly-L-lysine, which is coupled to synthetic peptides comprising T cell and B cell epitopes, preferably linked in tandem on the same branch (page 13). Epitopes of *P. falciparum* circumsporozoite protein (page 11, Table 1), such as $(NANP)_n$ (Table 1, "A") or "T1" (Table 1, "E"), are specifically taught for use. In contrast to the invention as instantly claimed, the reference does not teach a promiscuous T cell epitope for use in the MAP composition and, if necessary, does not teach coupling using oxime chemistry.

The teachings of Calvo-Calle et al. are as set forth previously and differ from the invention as instantly claimed in not teaching the universal T cell epitope as instantly claimed for use in the MAP composition and, if necessary, in not teach coupling using oxime chemistry.

Good et al. teach that a vaccine, e.g. one for *P. falciparum*, should have certain properties, including B cell epitopes covalently linked to T cell epitopes capable of being recognized by all who receive the vaccine (i.e. promiscuous). T cell epitopes should preferably derive from the organism of interest to provide for natural boosting (e.g. page 659). The reference teaches that the sequence $(NANP)_{n \geq 2}$ contains the B cell epitope of the circumsporozoite protein of *P. falciparum* (e.g. page 656).

Nardin et al. teach at least two "universal" T cell epitopes of *P. falciparum* circumsporozoite protein (pages 701-702 and 711-713) and teach their successful use linked to the $(NANP)_n$ B cell epitope for immunization of individuals having different class II major histocompatability complex molecules. The reference teaches SEQ ID NO: 3 as containing at least one T cell epitope recognized by T cells in sporozoite-immunized human patients (pages 702 or 713) which is presented by multiple class II human MHC molecules (pages 702, 706, or 713), and which is immunogenic when presented on sporozoites or in a MAP construct. The reference specifically suggests the epitope in vaccines (page 713). Moreover, the reference teaches immunization of "naive" human T cells with the similar sequence from the circumsporozoite protein from another isolate of *P. falciparum* (page 702). Further, the reference teaches instant SEQ ID NO: 3, not only as a universal T cell epitope for T helper cell responses, but also one which induces cytotoxic CD4+ T cells which may be involved in cellular mechanisms of anti-sporozoite immunity (page 704).

Rose et al. (WO 94/25071) or Rose et al. (Molecular Immunology 32: 1031, 1995) teach polyoximes as an alternative to the solid phase synthesized MAP compositions of Tam et al. for use in immunogenic compositions. The benefits of the modular polyoxime approach, including ease of preparation and purity of product, over the synthesis of MAPs by conventional solid-phase methods are taught. The dendritic polymer core of Tam et al., albeit modified, may be used as the backbone in the synthesis of the polyoxime immunogens (e.g. WO 94/25071, page 13).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have incorporated one or more T cell epitopes including a promiscuous T

cell epitope derived from the circumsporozoite protein of *P. falciparum*, as taught generally in Good et al. or specifically in Nardin et al., into the vaccine compositions of Tam et al. or Calvo-Calle et al. for use because any of Good et al., Tam et al., Calvo-Calle et al., or Nardin et al. suggest the incorporation of both T and B cell epitopes from the circumsporozoite protein of *P. falciparum* in synthetic vaccines for malaria, and either of Good et al. or Nardin et al. teach the importance of using promiscuous T cell epitopes linked to B cell epitopes in such an anti-malarial vaccine. If necessary, it would have been further obvious to have substituted a polymer formed via oxime chemistry for that taught in Tam et al., as modified, or in Calvo-Calle et al., as modified, in view of the specific suggestion to do so provided in either of Rose et al. (WO 94/25071) or Rose et al. (Molecular Immunology 32: 1031, 1995) for the benefits taught therein.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 6,669,945 B1. Although the conflicting claims are not identical, they are not patentable distinct from each other because the species and subgenus claims of the patent make obvious the species and genus claims of the instant application that recite immunogenic compositions, vaccines, or methods of use comprising universal T cell epitopes generically or comprising the identical species (SEQ ID NO: 3).

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Giane de Oliveira et al. disclose a multiple antigen peptide system comprising a B cell epitope ($(NANP)_3$) and a T cell epitope (T1) of the circumsporozoite protein of *Plasmodium falciparum* adsorbed to alum.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (571) 272-0821. The examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, SPE, can be contacted at (571) 272-0823.

The phone number for official facsimile transmitted communications to TC 1600, Group 1640, is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application, or requests to supply missing elements from Office communications, should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James L. Grun, Ph.D.
September 21, 2005

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